REMARKS

In the office action, the Examiner withdrew the anticipation rejection under 35 U.S.C. § 102(b) against claims 2, 4-6, 8, and 9 over Labrenz et al. (Science 290:1744-1747), maintained the anticipation rejection under 35 U.S.C. § 102(b) against claims 2, 4-6, 8, and 9 over Lou et al. (Clinical Chemistry 39:619-624, 1993), raised a new obviousness rejection under 35 U.S.C. § 103(a) against claims 7 and 10-12 over Lou et al. in view of Zhang et al. (BioFactors 15:27-38, 2001), and raised a new obviousness rejection under 35 U.S.C. § 103(a) against claims 52-56 and 58-66 over Zhang et al. Claims 26-30 and 57 were indicated to be allowable.

Each issue raised by the Examiner is addressed separately below. In view of the amendments noted above and the remarks below, applicants respectfully request reconsideration of the merits of this patent application.

A petition for two months extension of time accompanies this response so the response will be deemed to have been timely filed. If any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055. No other fee is believed to be due in connection with this response. However, if any fee is due in this or any subsequent response, please charge the fee to the same Deposit Account No. 17-0055.

Anticipation rejection under 35 U.S.C. § 102(b) over on Lou et al.

The Examiner rejected claims 2, 4-6, 8, and 9 as being anticipated by Lou et al. (Clinical Chemistry 39:619-624, 1993). Without agreeing with the rejection, applicants have canceled claim 4 and amended claims 2 and 6 to facilitate prosecution. Applicants reserve the right to pursue the canceled subject matter in a subsequent application.

Claims 2, 5, 6, 8, and 9 as amended limit the elemental selenium (Se(0)) particles to those having a diameter of 0.4 to 1 nanometer. A 37 C.F.R. § 1.132 declaration by lead inventor Dr. Fritz Sieber is submitted herewith to support that the Se(0) particles produced by the inventors have a diameter from about 0.4 to about 1 nanometer.

As described by Dr. Sieber in the declaration, there has been no good way of directly measuring Se(0) particles with a diameter of 1.8 nm or smaller (Se(0) particles in the size range of "Zhang et al. BioFactors 15:27-38, 2001" are well within the detection range of a standard

electron microscope). Dr. Sieber could not detect any signal from the Se(0) particles in his composition with electron microscopy combined with energy dispersive X-ray analysis (EDX), which has a resolution of 1.8 nm. However, Dr. Sieber proved through chemical analysis that Se(0) existed in his composition. This shows that the Se(0) particles in Dr. Sieber's composition is smaller than 1.8 nm. As it is well known in the art that 6-8 Se atoms are the smallest configurations for Se(0) and they form cyclical molecules with the largest dimension/diameter being about 1 nm and the smallest dimension/diameter being about 0.4 nm, Dr. Sieber concluded that the Se(0) particles produced and tested by Dr. Sieber are from about 0.4 nm to about 1 nm in diameter. In view of Dr. Sieber's declaration and given that Lou et al. did not disclose Se(0) particles having a diameter between 0.4 to 1 nm, applicants respectfully submit that claims 2, 5, 6, 8, and 9 as amended are not anticipated by Lou et al.

Obviousness rejection under 35 U.S.C. § 103(a) over Lou et al. in view of Zhang et al.

The Examiner rejected claims 7 and 10-12 as being obvious over Lou et al. (Clinical Chemistry 39:619-624, 1993) in view of Zhang et al. (BioFactors 15:27-38, 2001). Without agreeing with the rejection, claims 7, 10, and 11 have been amended to facilitate prosecution. Applicants reserve the right to pursue the canceled subject matter in a subsequent application.

Claims 7 and 10-12 as amended limit the elemental selenium (Se(0)) particles to those having a diameter of 0.4 to 1 nanometer. As discussed above, the attached 37 C.F.R. § 1.132 declaration by lead inventor Dr. Fritz Sieber showed that the Se(0) particles produced and tested by the inventors have a diameter from about 0.4 to about 1 nanometer. As already discussed in the response of February 6, 2006, the Se(0) particles disclosed by Lou et al. are at least 2 orders of magnitude larger than the size of Se(0) particles recited in the claims at issue. Zhang et al. disclose Se(0) particles of 20-60 nm (page 28, method 2.1). Neither Lou et al. nor Zhang et al. disclosed or suggested Se(0) particles of 0.4 to 1 nm. Neither of the references disclosed or taught a method that can produce Se(0) particles having a diameter from about 0.4 to about 1 nm. In view of the declaration submitted herewith, applicants respectfully submit that claims 7 and 10-12 as amended are not obvious over Lou et al. in view of Zhang et al.

Obviousness rejection under 35 U.S.C. § 103(a) over Zhang et al.

The Examiner rejected claims 52-56 and 58-66 as being obvious over Zhang et al. Without agreeing with the rejection, claims 52 is amended and claims 58-66 are canceled to facilitate prosecution. Applicants reserve the right to pursue the canceled claims and subject matter in a continuation application. Claim 52 as amended and its dependents (claims 53-56) are directed to a method of treating a human or non-human subject having cancer by administering a composition that comprises a pharmaceutically effective amount of Se(0) particles to the human or non-human subject. Applicants traverse the rejection in connection with claims 52-56 as amended in that Zhang et al. do not make it obvious to treat cancer with Se(0).

In making the rejection, the Examiner first alleged that Zhang et al. disclosed on page 27 that (1) Se, in several forms, suppresses the growth of tumor cells *in vivo* and *in vitro*, (2) consumption of 200 μg Se per day in cancer patients reduced mortality and depressed the incidence of many cancers including lung, colorectal and prostate cancers, and (3) Se is putative chemopreventative agent. However, Zhang et al. disclosed all above in connection with Se forms other than the oxidation-state-zero selenium (Se(0)) as recited in the claims at issue. For example, Zhang et al. cited four references to support point (1) above and these references teach the use of selenite, selenodiglutathione, l-selenomethionine, Se-methylselenocysteine, Se-propylselenocysteine, Se-allylselenocysteine, and organoselenium 1,4-phenylenebis(methylene) selenocyanate, but not Se(0). The reference (reference 9) cited by Zhang et al. to support point (2) above teaches the use of selenium-rich yeast extract (also called selenized yeast) that consists largely of selenomethionine, but not Se(0). Similarly, the reference (reference 14) cited by Zhang et al. to support point (3) above is a review article that cited 6 relevant references (references 1-6), all of which teach the use of other forms of Se, but not Se(0). In this regard, reference 1 mentions selenium in crops in general, which are mostly organic selenium; reference 2 teaches the use of H_2Se, sodium selenite, and two inorganic selenium compounds; reference 3 teaches the use of selenocysteine, selenomethionine, selenotrisulfides, and selenium-heavy metal complexes; reference 4 reports correlations between total amounts of selenium in soil and blood and the incidence of cancer; reference 5 teaches the use of selenite, selenocysteine, and selenomethionin; and reference 6 teaches the use of selenite, selenate, selenium dioxide, Se-cystine, Se-methionine, and Se-diglutathione.

Just because treating tumor cells and patients with other forms of Se may provide some beneficial effects does not make it obvious that Se(0) is useful in treating cancer. In fact, Zhang et al. may teach away from using Se(0) as it discloses, in consistent with the references cited therein, that "it is important to recognise that the biological activity of Se is an expression of Se in a wide variety of chemical forms, and not the element *per se*," i.e., Se(0) (p. 27, lines 4-6 under the section "1. Introduction").

In making the rejection, the Examiner further pointed out that Zhang et al. disclosed a composition comprising nano elemental Se that is prepared with BSA and the treatment of human hepatoma HepG2 cells with Se. In this regard, applicants note that just because an agent may kill cancer cells at a relative high concentration would not make it obvious that the agent is useful in treating cancer. Given at a sufficiently high dose, almost anything can kill cancer cells. In the experiment in which Zhang et al. tested the effect of Se(0) on cancer cells, it was shown that even at a very high concentration of 100 μM Se(0) did not kill human hepatoma HepG2 cells but only slowed down their growth (Fig. 6). Furthermore, the toxicity experiment of Zhang et al. conducted with mice showed that Se(0) is fairly toxic (Table 1, although less toxic than sodium selenite). Therefore, it would not have been obvious that Se(0) would be able to treat cancer at a dosage without killing the host. It is the inventors of the present invention who found that Se(0) preferentially kills cancer cells over normal cells and therefore is useful as an anticancer agent.

While the Se(0) data from Zhang et al. as discussed above does not make the present invention obvious, it is even more so in the context of the prior art as a whole. When evaluating the obviousness of a particular invention, the law requires considering the "whole" of the prior art. See In re Keller, 642 F.2d 413, 425 (CCPA 1981) (determining obviousness from "what the combined teachings of the references would have suggested to those of ordinary skill in the art"). "When prior art contains apparently conflicting references, the [PTO] must weigh each reference for its power to suggest solutions to an artisan of ordinary skill." See In re Young, 927 F.2d 588, 591 (Fed. Cir. 1991). As already discussed above, the references cited in Zhang et al. as a whole indicate that other forms of Se, not Se(0) *per se*, may be useful in cancer treatment and prevention. The limited Se(0) data presented by Zhang et al. is not sufficient overturn this understanding in the art to make the present invention obvious.

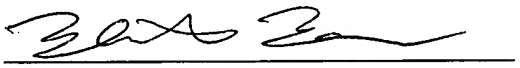
Furthermore, beyond looking to the prior art to determine if it suggests doing what the inventor has done, one must also consider if the art provides the required expectation of success. See In re Dow Chem. Co. v. American Cyanamid Co., 837 F.2d 469, 473 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be found in the prior art, not in applicant's disclosure." In this regard, even assuming for the sake of argument that one would try Se(0) for the treatment of cancer in view of Zhang et al., there would have been no reasonable expectation of success for the same reasons discussed above.

Accordingly, claims 52-56 as amended are not obvious over Zhang et al.

Summary

Having addressed each rejection raised by the Examiner, claims 26-30 and 52-57 as amended are believed to be in condition for allowance and a Notice of Allowance is respectfully requested. Should any issues remain outstanding, the Examiner is invited to contact the undersigned at the telephone number appearing below if such would advance the prosecution of this application.

Respectfully submitted,



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